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SPECIAL ARTICLE

The heart-brain connection: mechanistic insights and models

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Abstract While both cardiac dysfunction and progressive loss of cognitive function are prominent features of an ageing population, surprisingly few studies have addressed the link between the function of the heart and brain. Recent literature indicates that autoregulation of cerebral flow is not able to protect the brain from hypoperfusion when cardiac output is reduced or atherosclerosis is prominent. This suggests a close link between cardiac function and large vessel atherosclerosis on the one hand and brain perfusion and cognitive functioning on the other. Mechanistically, the presence of vascular pathology leads to chronic cerebral hypoperfusion, blood brain barrier breakdown and inflammation that most likely precede neuronal death and neurodegeneration. Animal models to study the effects of chronic cerebral hypoperfusion are available, but they have not yet been combined with cardiovascular models.

Keywords Cerebral hypoperfusion · Cardiovascular dysfunction · Cognitive decline · Neurodegeneration · Heart and brain

Dementia is one of the most common disorders among the elderly population and yet the pathogenesis of the disease is largely unknown. A connection between cardiovascular insults and cognitive decline is becoming evident from epidemiological studies such as the Framingham Heart Study and increasing knowledge on mechanistic insights highlights the importance of the heart-brain connection in the pathogenesis and progression of cognitive impairment.

In healthy individuals, sophisticated cerebrovascular control mechanisms, executed by the so-called neurovascular unit (an interplay between neurons, vascular cells, and glia), ensure that the brain's blood supply matches its energy requirements [1]. These requirements increase locally during neural activity, and they are met by a powerful local increase in blood flow due to a mechanism called neurovascular coupling or functional hyperaemia [2]. The cerebral vasomotor reactivity (CVR) keeps cerebral blood flow (CBF) relatively constant during changes of blood pressures, protecting the brain from unwanted swings in perfusion pressure [3]. However, the CVR is not always able to compensate for haemodynamic challenges. The most drastic example is acute arrest of CBF due to cardiac arrest [4], or the occlusion of a large cerebral artery, which leads to infarction of brain tissue. Apart from being overwhelmed, the efficacy of the CVR can be reduced by diseases affecting the neurovascular unit. Endothelium-dependent responses in the microcirculation may be impaired in atherosclerosis, hypertension, diabetes, and old age (discussed in Gorelick et al.[5]).

The amount of blood reaching the cerebral circulation may further depend on heart function and patency of the cerebropetal arteries. In patients with heart failure a reduced CBF was observed, and a reduced CBF correlated with a rising prevalence (of up to 25 %) of cognitive dysfunction [6, 7]. Even a subclinical decrease in cardiac output has been shown to be associated with impaired cognition [8], while improvement of heart function by cardiac transplantation or resynchronisation improved cognitive functioning [9–11]. These observations cannot be explained by the limited blood supply due to extracerebral factors if the CVR was normal. There is experimental evidence that reduced cardiac output hampers the CVR and reduces the spectrum of changes in systemic blood flow that it can handle, challenging cerebral perfusion [12]. More evidence for the assumption that insufficient blood supply to the cerebral circulation can lead to cognitive impairment comes from observations in patients with blocked internal carotid arteries [13]. About half of

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these patients were cognitively impaired [13, 14] which could not primarily be explained by structural brain damage, but rather by – potentially reversible – lactate accumulation in non-infarcted brain regions [15].

Atherosclerosis also affects the wall of cerebropetal arteries, playing an important role in vascular cognitive impairment (VCI). The risk of cognitive decline after coronary revascularisation procedures appears to be more closely linked to the degree of preoperative cerebrovascular disease than to the surgical procedure itself. Given that many candidates for a coronary artery bypass graft (CABG) have MRI evidence of cerebral infarction even before surgery [16], it is likely that the late cognitive decline previously reported in the literature is related to the progression of underlying cerebrovascular disease. Undiagnosed mild cognitive deficits are common in candidates for CABG even before surgery and may be a surrogate marker for underlying cerebrovascular disease [17]. In the Rotterdam study, intracranial carotid artery calcification measured by CT is present in more than 80 % of older white persons (mean age 69.6 years) [18] and is associated with conventional cardiovascular risk factors. Larger calcification volume, measured at four sites (coronary arteries, aortic arch, and extra- and intra-cranial carotid arteries) is associated with vascular brain disease (white matter lesion volume and cerebral infarcts), worse cognitive performance and relates to smaller brain tissue volumes and worse white matter microstructural integrity measured by MRI, revealing possible mechanisms through which atherosclerosis may lead to poorer cognition [19, 20]. Thus, there is ample epidemiological evidence that atherosclerosis affects the neurovascular unit. In addition, atherosclerosis can result in haemodynamic compromise based on steno-occlusive disease and plaque rupture with thrombotic occlusion of large arteries and emboli originating from ruptured plaques [5].

Animal models that enable dissection of the exact molecular mechanism involved in the heart-brain connection include the bilateral cuff or coil-induced carotid artery stenosis (BCAS), and the transverse aortic ligation (TAC). The BCAS model is a model of chronic cerebral hypoperfusion induced by placement of microcoils around both carotid arteries [21]. In this model a reduced CBF, activation of microglia and astroglia, white matter lesions, grey matter changes, hippocampal atrophy and micro-infarcts have been described [21–25]. TAC, the ligation of the aortic arch between the carotids, is a mouse model of chronic heart failure leading to a reduced ejection fraction [26, 27]. The TAC model shows enhanced blood brain barrier (BBB) permeability and NAD(P)H oxidase activity as well as inflammation and reduced CBF [28, 29]. Interestingly altered kinetics of amyloid beta have been described in both models [30–32] potentially linking neurodegenerative and neurovascular mechanisms. Classical mouse models of atherosclerosis, such as the ApoE−/− mouse, also show an enhanced BBB permeability, inflammation, endothelial activation and reduced clearance of amyloid beta protein, but the link with cardiac function and cerebral flow has not been described yet and needs further investigation to elucidate the role of cardiovascular insults in neurodegeneration.

From the mechanistic perspective, dysfunction of the neurovascular unit that forms the BBB plays a central role in the heart-brain connection. Neurovascular unit dysfunction is associated with activated endothelial cells, disrupted pericytes, and abnormal endothelial-endothelial and endothelial-pericyte connections. This induces leakage of plasma constituents and infiltration of inflammatory cells into the surrounding tissue (discussed by Zlokovic [33]). Reactive oxygen species and inflammation are thought to play a major role in stimulating these responses. Oxidative stress induces endothelial dysfunction, opening of the BBB, and cytokine production [34]. Inflammation, in turn, enhances oxidative stress by upregulating the expression of reactive oxygen species-producing enzymes and downregulating antioxidant defences [35]. Furthermore, oxidative stress and inflammation compromise the repair mechanism of the damaged white matter, by interfering with proliferation, migration and differentiation of oligodendrocyte progenitor cells [36–38]. The loss of growth factors produced by the brain, which has been observed in both Alzheimer's disease and VCI, further compromises repair mechanisms [39]. These mechanisms affect cerebral arterioles in particular and can contribute to the development of small vessel diseases such as cerebral amyloid angiopathy and (hypertension related) arteriolosclerosis. Pericytes play a critical role in the regulation of the BBB function [40] and may have destructive inflammatory responses [41]. Bell and colleagues reported that expression of ApoE4 and lack of murine ApoE, but not ApoE2 and ApoE3, leads to BBB breakdown by activating a proinflammatory pathway in pericytes involving cyclophilin A–nuclear factor-κB–matrix-metalloproteinase-9. The BBB breakdown subsequently leads to neuronal uptake of blood-derived neurotoxic proteins, and microvascular and CBF reductions. Notably, the vascular defects developed before neuronal changes and dysfunction occurred suggesting that vascular defects can initiate neurodegenerative changes.

To conclude, there is emerging evidence supporting a link between cerebral haemodynamic impairment and cognitive function. Cardiac failure, atherosclerosis, steno-occlusive and small artery diseases affect the blood supply to the brain, most likely affecting the function of the neurovascular unit and BBB. A disrupted BBB causes inflammation, oxidative stress and exposes neurons to neurotoxic proteins. The exact pathophysiological mechanisms and causative relationships remain to be investigated. Animal models of chronic cerebral hypoperfusion such as TAC and BCAS have become available, but need to be combined with cardiovascular models.

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